Angiotensin Modulators: Angiotensin II Receptor Blockers Therapeutic Class Review (TCR)

September 1, 2017

Magellan Rx Management
Attention: Legal Department
6950 Columbia Gateway Drive
Columbia, Maryland 21046

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Angiotensin II Receptor Blockers: Single Agents		
azilsartan (Edarbi®)[1]	Arbor	▪ Hypertension
candesartan (Atacand®)[2]	generic, AstraZeneca	▪ Hypertension (including ages 1 to < 17 years) ▪ Heart failure – (LVEF <40%, NYHA II-IV) to reduce risk of CV death and reduce hospitalizations for heart failure (in addition to ACE inhibitors or when ACE inhibitors are not tolerated)
eprosartan[3]	Mylan	▪ Hypertension
irbesartan (Avapro®)[4]	generic, Sanofi-Aventis	▪ Hypertension ▪ Nephropathy in type 2 diabetic patients
losartan (Cozaar®)[5]	generic, Merck	▪ Hypertension (including ages 6 to 16 years) ▪ Nephropathy in type 2 diabetic patients ▪ Reduce the risk of stroke in hypertensive patients with LVH (not in African American patients)
olmesartan (Benicar®)[6]	generic, Daiichi Sankyo	▪ Hypertension
telmisartan (Micardis®)[7]	generic, Boehringer Ingelheim	▪ Hypertension ▪ 80 mg tablets only: risk reduction of myocardial infarction (MI), stroke, or death from CV causes in patients ≥ 55 years at high risk of developing major CV events who are unable to take ACE inhibitors
valsartan (Diovan®)[8]	generic, Novartis	▪ Hypertension (including ages 6 to 16 years) ▪ Heart failure (NYHA II-IV) to reduce CHF hospitalizations ▪ Reduction of CV mortality in clinically-stable patients with left ventricular failure or left ventricular dysfunction following MI
Angiotensin II Receptor Blockers: Combination Products		
azilsartan/chlorthalidone (Edarbyclor®)[9]	Arbor	▪ Hypertension (first-line therapy in patients requiring multiple agents)
candesartan/HCTZ (Atacand HCT®)[10]	generic, AstraZeneca	▪ Hypertension
irbesartan/HCTZ (Avalide®)[11]	generic, Sanofi-Aventis	▪ Hypertension (first-line therapy in patients requiring multiple agents)
losartan/HCTZ (Hyzaar®)[12]	generic, Merck	▪ Hypertension (first-line therapy in setting of prompt BP reduction) ▪ Reduce the risk of stroke in hypertensive patients with LVH (not in African American patients)
olmesartan/HCTZ (Benicar HCT®)[13]	generic, Daiichi Sankyo	▪ Hypertension
sacubitril/valsartan (Entresto®)[14]	Novartis	▪ Reduce CHF hospitalizations in patients with heart failure (NYHA II-IV) and reduced ejection fraction
telmisartan/HCTZ (Micardis HCT®)[15]	generic, Boehringer Ingelheim	▪ Hypertension
valsartan/HCTZ (Diovan HCT®)[16]	generic, Novartis	▪ Hypertension (first-line therapy in patients requiring multiple agents)

ACE inhibitors = angiotensin converting enzyme inhibitors; CV = cardiovascular; HCTZ = hydrochlorothiazide; LVH = left ventricular hypertrophy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association Classification

Brand Teveten® and Teveten HCT® were discontinued as of August 2015. There is no generic for eprosartan/HCTZ (Teveten HCT).

OVERVIEW

Approximately 75 million (32%) adults in the United States have hypertension; the highest prevalence is among African American men and women at 43% and 45.7%, respectively.[17,18] It is estimated that hypertension is controlled in only 54% of patients with the condition. Hypertension is an independent risk factor for cardiovascular disease and can lead to heart failure (HF) and stroke if uncontrolled for a prolonged period.[19] Angiotensin receptor blockers (ARBs) are indicated for the treatment of hypertension either alone or in combination with other antihypertensive medications.

Hypertension

The 2014 Eighth Report from the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8) in general recommends to start antihypertensive therapy in patients at least 60 years of age when systolic blood pressure (SBP) 150 mm Hg or greater or diastolic blood pressure (DBP) is 90 mm Hg or greater, with a goal of SBP < 150 mm Hg and DBP < 90 mm Hg.[20] For patients younger than 60 years and adults with chronic kidney disease (CKD), therapy should be initiated when SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg and target blood pressure is less than 140/90 mm Hg. In the non-African American population, initial treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme (ACE) inhibitor or ARB. For African Americans, initial treatment should include a thiazide-type diuretic or CCB. In patients with CKD treatment should include an ACE inhibitor or ARB to improve kidney function, regardless of race or diabetes status. If blood pressure goal is not reached within 1 month of starting treatment, the dose should be increased or a second a drug from another class should be added; a third drug can be added if needed.

The American College of Physicians (ACP) and American Academy of Family Physicians (AAFP) published evidence-based recommendations on the benefits and harms of higher (< 150 mm Hg) versus lower (< 140 mm Hg) SBP targets in the treatment of hypertensive adults ages 60 years and older.[21] The ACP and AAFP recommend initiating antihypertensive therapy in adults 60 years and older with SBP ≥ 150 mm Hg with a target SBP < 150 mm Hg to reduce the risk of mortality, stroke, and cardiac events (strong recommendation, high-quality evidence). A stricter goal of SBP < 140 mm Hg may be considered in older adults with a history of stroke or transient ischemic attack to reduce the risk for recurrent stroke (weak recommendation, moderate-quality evidence). A stricter goal, SBP < 140 mm Hg, may also be considered in older adults at high cardiovascular (CV) risk to reduce the risk of stroke or cardiac events (weak recommendation, moderate-quality evidence). The clinician and patient should discuss the risk versus benefit when determining the most appropriate blood pressure goal. The ACP and AAFP also state that providers should consider treatment with nonpharmacologic options (e.g., weight loss, diet, exercise), as well as pharmacologic therapy. Treatment burden (e.g., total number of drugs prescribed, drug interactions, adverse effects), given the potential for other comorbid conditions, should also be taken into consideration when treating hypertensive older adults. If pharmacologic therapy is chosen, generic formulations should be prescribed, when available, to reduce cost and thereby aid treatment adherence.

It is estimated that 3.5% of children and adolescents have hypertension.[22] In 2017, American Academy of Pediatrics (APP) published guidelines on diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. The goal of treatment is to achieve a blood pressure that decreases the risk for organ damage in youth and decrease the risk of hypertension in adulthood. For children and adolescents on treatment for HTN, the blood pressure goal is < 90th percentile and < 130/80 mmHg. Lifestyle modifications such as diet and physical exercise are recommended for the potential benefit to reduce blood pressure. First line therapy options include an ACE inhibitor, ARB, long-acting calcium channel blocker, or thiazide diuretic; treatment should begin a low dosage and titrate as needed; a second agent may be added if needed. Beta blockers are not recommended as initial pharmacologic treatment in children due to the side effect profile and to follow the therapy recommendations of beta blockers in adults. Long-term studies on the safety of antihypertensive medications in children and their impact on future cardiovascular disease are limited.

Heart Failure

According to the 2013 American College of Cardiology (ACC) and American Heart Association (AHA) consensus guidelines for the management of HF, routine combined use of an ACE inhibitor and a beta-blocker is recommended in all patients with reduced ejection fraction heart failure (HF*r*EF), unless contraindicated.[23] Drugs with an indication for HF include many ACE inhibitors and some beta-blockers. ARBs that are indicated for HF when a patient is intolerant to an ACE inhibitor include candesartan (Atacand) and valsartan (Diovan). In addition, for patients with HF*r*EF, diuretics are recommended if fluid retention is present; aldosterone antagonists (spironolactone [Aldactone®] and eplerenone [Inspra®]) are recommended in patients who also have adequate renal function; and digoxin can be beneficial to decrease hospitalizations due to HF. The combination of hydralazine and isosorbide dinitrate is recommended in African Americans with HF*r*EF who are persistently symptomatic with the use of an ACE inhibitor and a beta-blocker. The ACC/AHA also recommends the use of ARBs in patients unable to tolerate an ACE inhibitor and in patients with HF following a non-ST-elevated myocardial infarction (NSTEMI) or ST-elevated myocardial infarction (STEMI).[24,25]

In 2015, the Food and Drug Administration (FDA) approved sacubitril/valsartan (Entresto), the combination product of a neprilysin inhibitor and an ARB, also called an angiotensin receptor-neprilysin inhibitor (ARNI), which has demonstrated greater efficacy than enalapril in patients with HF*r*EF.[26] In the 2016 ACC/AHA/Heart Failure Society of America (HFSA) Focused Update on New Pharmacologic Therapy for Heart Failure, which updates the 2013 ACCF/AHA guideline on the management of HF, the role of sacubitril/valsartan (Entresto) has been addressed.[27] The guidance recommends an ACE inhibitor, ARB, or ARNI in addition to a beta-blocker and aldosterone (in select patients) in patients with chronic HF*r*EF (Class I, Level A [ACE inhibitor, ARB] and B-R [ARNI] evidence). Patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or an ARB should be switched to an ARNI to further reduce morbidity and mortality (Class I, Level B-R evidence). An ARNI should not be administered concomitantly or within 36 hours of an ACE inhibitor or in patients with a history of angioedema. These recommendations are primarily based on the results of the PARADIGM-HF trial in which an ARNI (sacubitril/valsartan) was found to be superior to enalapril in reducing the risks of death and hospitalization for heart failure.[28] A second update to the 2013 ACC/AHA consensus guidelines for the management of HF was published by ACC/AHA/HFSA in 2017 and focuses on revisions to select other subsections in the 2013 guidelines. Notably, this revision reiterates the recommendation in the 2016 update regarding the use of ACE inhibitors, ARBs, and the ARNI in the treatment of patients with chronic HF*r*EF. ARBs are recommended over an ACE inhibitor in those intolerant to an ACE inhibitor.

Nephropathy

Approximately 25% of patients with diabetes will develop microalbuminuria during the 10 years after diagnosis and 25% to 40% will develop diabetic nephropathy over 20 to 25 years after diabetes onset.[29]

Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in the U.S., accounting for 40% of all the patients with end-stage renal disease (ESRD) who are on dialysis.[30] Type 1 and 2 diabetes increase the risk for nephropathy and follow the same progression to renal insufficiency and failure. Guidelines by the American Diabetes Association (ADA; 2017), American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE; 2015/2017), the AHA/American Stroke Association (ASA; 2014), and the JNC-8 suggest that all patients with diabetes should receive an ACE inhibitor or ARB for the treatment of hypertension to reduce the risk of stroke and to delay the progression of diabetic nephropathy.[31,32,33,34,35,36]

In patients with type 1 diabetes, hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy, hypertension, and microalbuminuria; both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria in patients with type 2 diabetes. In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine > 1.5 mg/dL), ARBs have been shown to delay the progression of nephropathy. Irbesartan (Avapro) and losartan (Cozaar) are approved to slow the progression of nephropathy in type 2 diabetic patients. Prevention of nephropathy progression is associated with reduced healthcare costs and improvement in mortality. ACE inhibitors have clearly shown to prevent early death in diabetic patients. Telmisartan (Micardis) and ramipril (Altace®) were similar in reducing cardiovascular (CV) mortality in patients with vascular disease or high-risk diabetes; however, the combination of telmisartan and ramipril resulted in more adverse events without increased benefit.[37]

Myocardial infarction

In the setting of acute myocardial infarction (AMI), ACE inhibitors have been shown to reduce mortality rates even in those with normal left ventricular function.[38,39] ACE inhibitors should be started and continued indefinitely in all patients recovering from ST-elevation myocardial infarction (STEMI) or unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI) with left ventricular ejection fraction (LVEF) of 40% or less and for those with hypertension, diabetes, or CKD, unless otherwise contraindicated. ACE inhibitors are also considered a reasonable option in patients who are at lower risk. ARBs are recommended in place of ACE inhibitors in those who are intolerant to ACE inhibitors.

The Agency for Healthcare Research and Quality (AHRQ) has published a comparative effectiveness report for the ACE inhibitors, ARBs, and aliskiren.[40] The ACE inhibitors and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension. It is possible that aliskiren may be more effective than ACE inhibitors (ramipril), but no differences were found in studies when compared to an ARB (losartan). For mortality and major cardiovascular events, there is insufficient evidence to determine if there are any different effects of ACE inhibitors versus ARBs on these serious outcomes. ACEIs have been shown to have a greater risk of cough than ARBs and the direct renin inhibitor.[41,42,43]

ARBs are available as fixed-dose combinations with a diuretic to treat hypertension.

PHARMACOLOGY[44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63]

All ARBs are available as single agents and in combination with a thiazide diuretic such as hydrochlorothiazide (HCTZ) or chlorthalidone. Valsartan is also available in combination with a neprilysin inhibitor, sacubitril.

ACE inhibitors do not completely block the renin-angiotensin-aldosterone system (RAAS). ACE inhibitors are competitive inhibitors of angiotensin-converting enzyme, which converts angiotensin I to angiotensin II, a potent vasoconstrictor. Angiotensin II causes vasoconstriction, release of aldosterone and antidiuretic hormone, sympathetic activation, and constriction of the efferent arterioles of the glomerulus in the kidneys. ARBs block the vasoconstrictive and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, such as vascular smooth muscle and the adrenal gland. Non-ACE pathways also produce angiotensin II. ARBs do not inhibit ACE (kinase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin).

Angiotensin receptor-neprilysin inhibitors (ARNIs) increase levels of natriuretic peptides that are degraded by neprilysin through inhibition of neprilysin and simultaneously inhibit the effects of angiotensin II. The ultimate result of sacubitril's neprilysin inhibition is vasodilation, natriuresis, and diuresis.

Thiazide diuretics, such as HCTZ, exhibit its pharmacological effects by blocking the reabsorption of sodium and chloride leading to diuresis and a reduction in intravascular volume. Consequently, there are increases in plasma renin activity and aldosterone secretion. Concurrent administration of an ARB and a thiazide diuretic may help to decrease potassium loss that occurs with thiazide diuretic therapy.

Chlorthalidone, a thiazide-like diuretic, produces diuresis with increased excretion of sodium and chloride. The site of action appears to be the cortical diluting segment of the ascending limb of Henle's loop of the nephron. The diuretic effects of chlorthalidone lead to decreased extracellular fluid volume, plasma volume, cardiac output, total exchangeable sodium, glomerular filtration rate, and renal plasma flow. Although the mechanism of action of chlorthalidone and related drugs is not fully clear, sodium and water depletion appear to provide a basis for its antihypertensive effect.

PHARMACOKINETICS[64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80]

Drug	Prodrug	Time to Peak (h)	Bioavailability (%)	Food – Peak Levels	Food – AUC	Elimination Half-life (h)	Elimination Altered in Renal Dysfunction	Elimination Altered in Hepatic Dysfunction
Angiotensin II Receptor Blockers								
azilsartan (Edarbi)	Yes*	1.5–3	60	No effect	No effect	11	No	No
candesartan (Atacand)	Yes†	3–4	15	--	No effect	9	Yes	No
eprosartan	No	1–2	13	< 25%	< 25%	20	Yes	Yes§
irbesartan (Avapro)	No	1.5–2	60–80	No effect	No effect	11–15	No	No
losartan (Cozaar)	Yes‡	1 / 3–4	33	Decreased	↓ 10%	2 / 6-9‡	No	Yes
olmesartan (Benicar)	Yes	1–2	26	No effect	No effect	13	Yes§	Yes§
telmisartan (Micardis)	No	0.5–1	42–58 dose dependent	--	↓ 6–20%	24	No	Yes
valsartan (Diovan)	No	2–4	25	↓ 50%	↓ 40%	6	No	No
Components in Combination Products								
chlorthalidone	No	1.5–6	65	No effect	No effect	40–60	Yes	No
HCTZ	No	1–5	65–75	↓ 20%	--	5–18	Yes	No
sacubitril	No	0.5–2	≥ 60	No effect	No effect	1.4–11.5 (metabolite)	Yes	Yes§

* azilsartan medoxomil – active metabolite is azilsartan

† candesartan cilexetil – active metabolite is candesartan

‡ losartan – active metabolite is EXP3174

§ dosage adjustments are not necessary

CONTRAINDICATIONS/WARNINGS[81,82,83,84,85,86,87,88,89,90,91,92,93,94, 95,96,97]

Hypersensitivity to any angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) is a contraindication. The HCTZ component in the combination agents is contraindicated in patients with anuria or a sulfa allergy. Azilsartan/chlorthalidone (Edarbyclor) is contraindicated in patients with anuria.

An ARB or an ARNI (Entresto) should not be prescribed with an ACE inhibitor. Aliskiren and aliskiren-containing products are contraindicated with ARBs, or ACE inhibitors, in patients with diabetes due to increased risk of renal impairment, hyperkalemia, and hypotension. Do not co-administer aliskiren with an ARB in patients with diabetes. Avoid use of aliskiren with ARBs in patients with renal impairment (estimated glomerular filtration rate [GFR] < 60 mL/min/1.73 m^2).

ARBs should be used with caution in patients that are volume and salt depleted, have hyperkalemia, or have unilateral and bilateral renal artery stenosis. Volume or salt depletion should be corrected prior to administration. Concomitant use of an ARB with drugs that may increase potassium levels may increase the risk of hyperkalemia; serum potassium should be monitored periodically.

The FDA evaluated data from 2 clinical trials in which patients with type 2 diabetes taking olmesartan (Benicar) had a higher rate of death from a cardiovascular (CV) cause compared to placebo.[98] In both the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) and Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) trials, patients with type 2 diabetes were given either olmesartan or placebo to determine if treatment with olmesartan would slow the progression of kidney disease. An unexpected finding observed in both trials was a greater number of deaths from a CV cause (MI, sudden death, or stroke) in the olmesartan-treated patients compared to placebo. The FDA has completed its safety review of patients with type 2 diabetes taking olmesartan and found no clear evidence of a higher rate of CV risk as compared to placebo.[99] The FDA reminds practitioners that numerous clinical trials with olmesartan, as well as trials with other ARBs, have not suggested an increased risk of CV-related death. Currently, the FDA still believes that the benefits of olmesartan in patients with hypertension continue to outweigh the potential risks.

Sprue-like enteropathy has been reported in patients taking olmesartan months to years after the start of the drug. Severe, chronic diarrhea with substantial weight loss has been reported and, if a patient develops these symptoms while on olmesartan, other etiologies must be excluded. Discontinuing olmesartan in cases where no other etiologies are identified should be considered. In July 2010, the FDA announced that they were conducting a review of ARBs after a meta-analysis including data from over 60,000 patients suggested that ARBs may be associated with a small increased risk of cancer.[100] In June 2011, the study was complete, and the FDA concluded that treatment with an ARB does not increase cancer risk.[101] To draw this conclusion, the FDA conducted a trial-level meta-analysis of 31 clinical trials in which patients were randomized to treatment with an ARB (n=84,461) or a non-ARB (n=71,355). The meta-analysis evaluated the association between ARBs and the risk of incident (new) cancer, cancer-related death, breast cancer, lung cancer, and prostate cancer. The rate of cancer events in the ARB group was 1.82 per 100 patient-years compared to 1.84 per 100 patient-years in non-ARB comparators. The relative risk of cancer in patients taking ARBs was 0.99 (95% confidence interval [CI], 0.92 to 1.06). The FDA also found no evidence of association between ARBs and cancer-related death (relative risk, 1.04; 95% CI, 0.96 to 1.13), breast cancer (odds ratio [OR], 1.06; 95% CI, 0.9

to 1.23), lung cancer (OR, 1.07, 95% CI, 0.89 to 1.29), or prostate cancer (OR, 1.05; 95% CI, 0.95 to 1.17).

Another meta-analysis assessed the association between antihypertensive drugs and cancer risk.[102] It included 70 randomized controlled trials with 324,168 participants and recorded no difference in the risk of cancer with ARBs. There was an increased risk with the combination of ACE Inhibitors plus ARBs (OR, 1.14; 95% CI, 1.02 to 1.28); however, this risk was not apparent in the random-effects model (OR, 1.15; 95% CI, 0.92 to 1.38).

Thiazide diuretics which are commonly used in combination with ARBs may cause exacerbation or activation of systemic lupus erythematosus. Thiazide diuretics may also cause electrolyte (e.g., hypercalcemia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, hyponatremia, and hyperuricemia) or fluid imbalances; monitoring is recommended.

Hydrochlorothiazide can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms, such as acute onset of decreased visual acuity or ocular pain, can occur within hours to weeks of drug initiation. If untreated, acute angle-closure glaucoma can lead to permanent vision loss. Hydrochlorothiazide should be discontinued as rapidly as possible. Prompt medical or surgical treatments may be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

DRUG INTERACTIONS[103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119]

Significant drug interactions have not been reported with ARBs; however use with potassium-sparing diuretics, potassium supplements, or other drugs that may increase potassium levels can lead to hyperkalemia. Potassium levels should be monitored in these patients. Increases in serum lithium concentrations and lithium toxicity have been reported with concurrent use of lithium and ARBs. Serum lithium levels should be monitored with concurrent use. In addition, diuretics, including hydrochlorothiazide (HCTZ) reduce the renal clearance of lithium and greatly increase the risk of lithium toxicity. These agents generally should not be given concurrently.

Administration of a nonsteroidal anti-inflammatory drug (NSAID) can reduce the diuretic, natriuretic, and antihypertensive effects of HCTZ and ARBs. Cholestyramine and colestipol resins bind HCTZ and reduce its absorption from the gastrointestinal tract. Also, the HCTZ dose should be staggered (4 hours prior or 4 or 4 to 6 hours after) from resin administration. Dosage adjustment of the antidiabetic drug may be required if given with HCTZ. Administration of carbamazepine and HCTZ may lead to symptomatic hyponatremia. In patients who are elderly, volume-depleted (including those on diuretic therapy), or who have compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ARBs, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving ARBs and NSAID therapy. Concomitant use of steroids or adrenocorticotropic hormone (ACTH) with HCTZ may lead to hypokalemia.

In addition, HCTZ may increase the hyperglycemic effect of diazoxide and decrease the renal excretion of methotrexate and cyclophosphamide resulting in an increased myelosuppressive effect. Cyclosporine, when used with HCTZ, may increase the risk of hyperuricemia. HCTZ may decrease arterial responsiveness to norepinephrine, but this does not preclude its use if a pressor is needed.

Drug interactions with the combination product sacubitril/valsartan are the same as those described above due to the ARB component and effect of neprilysin inhibition.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with ARBs, angiotensin-converting enzyme (ACE) inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on an ARB and other agents that affect the RAAS.

The ALTITUDE study, a phase 3, double-blind trial evaluated the use of aliskiren in addition to conventional therapy in patients with type 2 diabetes and renal impairment, who are at high risk of cardiovascular and renal events.[120] Patients (n=8,606) were randomized to receive either aliskiren 300 mg or placebo, in addition to conventional therapy, including an ACE inhibitor or ARB. The study was halted early. The Data Monitoring Committee identified a higher incidence of non-fatal stroke, renal complications, hyperkalemia, and hypotension after 18 to 24 months of therapy in the aliskiren arm of the study. The study sponsor, Novartis, recommended that ALTITUDE investigators remove aliskiren-based products from their patients' treatment regimen and review their high blood pressure medication. Novartis is also reviewing the findings of other clinical studies involving aliskiren and combination therapies. Novartis recommends healthcare professionals should stop aliskiren-containing medications in diabetic patients who are also taking an ACE inhibitor or an ARB. Alternative antihypertensive therapy should be considered.

ADVERSE EFFECTS[121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137]

All ARBs have been well tolerated in clinical trials, with an incidence of adverse effects comparable to placebo. Cough and hyperkalemia, which have been problematic with angiotensin-converting enzyme (ACE) inhibitors, do not appear to occur as frequently with the ARBs.

Angioedema has been reported with all ARBs, and the risk appears to be lower than with ACE inhibitors.[138]

Drug	Dizziness	Angioedema	Back Pain	URI	Discontinuation Rate
azilsartan (Edarbi)	≥ 0.3	reported	nr	nr	2.2–2.7 (2.4)
candesartan (Atacand) n=3,260 (n=1,106)	4 (3)	< 1	3 (2)	6 (4)	3.3 (3.5)
eprosartan	≥ 1	reported	< 1	8 (5)	4 (6.5)
irbesartan (Avapro)	≥ 1	< 1	nr	nr	3.3 (4.5)
losartan (Cozaar) n=1,075 (n=334)	3 (2)	< 1	2 (1)	8 (7)	2.3 (3.7)
olmesartan (Benicar)	3 (1)	reported	> 1	nr	2.4 (2.7)
sacubitril/valsartan (Entresto)	6	reported	nr	nr	reported
telmisartan (Micardis) n=1,455 (n=380)	≥ 1	reported	3 (1)	7 (6)	nr
valsartan (Diovan) n=2,316 (n=888)	> 1	reported	> 1	> 1	2.3 (2)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported. URI = upper respiratory infection

Adverse reactions commonly reported with chlorthalidone and hydrochlorothiazide (HCTZ) include hyperuricemia and electrolyte abnormalities (e.g., hypokalemia, hyponatremia). Other adverse effects reported with chlorthalidone and HCTZ may occur when used as a fixed-dose combination product with an ARB, as found in this class.

SPECIAL POPULATIONS[139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,,155,156]

Pediatrics

Losartan (Cozaar), olmesartan (Benicar), and valsartan (Diovan) are indicated for the treatment of hypertension in children ages 6 to 16 years. Candesartan (Atacand) is indicated for the treatment of hypertension in children ages 1 to < 17 years of age. Candesartan use in pediatric patients with a glomerular filtration rate < 30 mL/min/1.73 m^2 have not been studied. Also, candesartan doses above 0.4 mg/kg or 32 mg have not been studied in this population. Safety and effectiveness in the pediatric population have not been established for the other ARBs.

Safety and efficacy of azilsartan (Edarbi), azilsartan/chlorthalidone (Edarbyclor), sacubitril/valsartan (Entresto), and hydrochlorothiazide (HCTZ) have not been established in children.

Geriatrics

In general, no relevant pharmacokinetic differences for any drug in this review have been observed in geriatric patients (age ≥ 65 years) compared to younger adults; however, caution should be used in this population due to the blood pressure lowering effects of these agents. In addition, a greater sensitivity of this population cannot be ruled out.

Pregnancy

All products in this review carry a boxed warning for fetal toxicity. When pregnancy is detected, discontinue medication as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus, particularly during the second and third trimesters.

Race

Losartan (Cozaar) and losartan/hydrochlorothiazide (Hyzaar) are both indicated for the reduction of the risk of stroke in hypertensive patients with left ventricular hypertrophy. However, beneficial effects have not been seen in the African American population. In general, antihypertensive benefits may be smaller in the African American population, as they are often a low-renin population.

Renal Impairment

Renin-angiotensin-aldosterone (RAAS) system blockers, including ARBs, may cause renal failure in susceptible patients, such as those with renal artery stenosis.

No specific dosage adjustments are recommended for ARBs in patients with renal impairment for most agents, but lower starting doses and maximum may be considered. However, data are limited in severe renal impairment. Patients should be monitored for potentiation of effects. The maximum dose of eprosartan in severe renal impairment is 600 mg/day. In addition, dosage adjustment is required for sacubitril/valsartan with severe renal impairment.

Chlorthalidone and HCTZ should be used with caution in renal impairment as they may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Hepatic Impairment

No specific dosage adjustments are recommended in patients with hepatic impairment for most agents, but lower starting and maximum doses may be considered. However, data are limited in severe hepatic impairment. Patients should be monitored for potentiation of effects. Losartan and telmisartan should be started at a lower dose in patients with hepatic impairment. In addition, dosage adjustment is required for sacubitril/valsartan with moderate hepatic impairment; use is not recommended in patients with severe hepatic impairment.

Thiazide diuretics should be used with caution in patients with impaired hepatic function since minor fluid and electrolyte imbalances may precipitate hepatic coma.

DOSAGES[157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173]

Drug	Initial hypertension dosage	Hypertension dosage range	Type 2 diabetic nephropathy dosage range	Risk Reduction	CHF	Post MI	Dose for volume- or salt-depleted patients	Availability
Angiotensin II Receptor Blockers: Single Agents								
azilsartan (Edarbi)	80 mg once daily	40 mg to 80 mg once daily	--	--	--	--	no dosage recommendation	40 mg, 80 mg tablets
candesartan (Atacand)	16 mg once daily; Pediatrics: 1 to < 6 years: 0.2 mg/kg once daily; 6 to < 17 years: < 50 kg weight: 4 mg to 8 mg once daily; > 50 kg weight: 8 mg to 16 mg once daily*	8 mg to 32 mg; Pediatrics: 1 to < 6 years: 0.05 to 0.4 mg/kg daily; 6 to < 17 years: < 50 kg weight: 4 mg to 16 mg daily; > 50 kg weight: 4 mg to 32 mg daily May give doses divided once or twice daily	--	--	4 mg to 32 mg once daily	--	no dosage recommendation†	4 mg, 8 mg, 16 mg, 32 mg tablets
eprosartan	600 mg once daily	400 mg to 800 mg per day; divided doses once or twice daily	--	--	--	--	no dosage recommendation†	600 mg tablets
irbesartan (Avapro)	150 mg once daily	75 mg to 300 mg once daily	300 mg once daily	--	--	--	75 mg once daily	75 mg, 150 mg, 300 mg tablets
losartan (Cozaar)	50 mg once daily Pediatrics (6 to 16 years): 0.7 mg/kg/day (or 50 mg daily)	25 mg to 100 mg per day; divided doses once or twice daily Pediatrics (6 to 16 years): 0.7 mg/kg/day (or 50 mg daily) to max of 1.4 mg/kg/day or 100 mg daily	50 mg to 100 mg once daily	Reduction of stroke risk with HTN and LVH: 50 mg to 100 mg daily	--	--	25 mg once daily	25 mg, 50 mg, 100 mg tablets

Dosages (continued)

Drug	Initial hypertension dosage	Hypertension dosage range	Type 2 diabetic nephropathy dosage range	Risk Reduction	CHF	Post MI	Dose for volume- or salt-depleted patients	Availability
Angiotensin II Receptor Blockers: Single Agents *(continued)*								
olmesartan (Benicar)	20 mg once daily Pediatrics (6 to 16 years): < 35 kg 10 mg once daily; ≥ 35 kg 20 mg once daily*	20 mg to 40 mg once daily Pediatrics (6 to 16 years): < 35 kg 10 to 20 mg once daily; ≥ 35 kg 20 to 40 mg once daily*	--	--	--	--	no dosage recommendation†	5 mg, 20 mg, 40 mg tablets
telmisartan (Micardis)	40 mg once daily	20 mg to 80 mg once daily	--	CV risk reduction: 80 mg once daily	--	--	no dosage recommendation†	20 mg, 40 mg, 80 mg tablets
valsartan (Diovan)	80 mg to 160 mg once daily	80 mg to 320 mg once daily Pediatrics (6 to 16 years): 1.3 to 2.7 mg/kg once daily (40 mg to 160 mg)	--	--	40 mg to 160 mg twice daily	20 mg to 160 mg twice daily	no dosage recommendation†	40 mg, 80 mg, 160 mg, 320 mg tablets
Angiotensin II Receptor Blockers: Combination Products								
azilsartan/ chlorthalidone (Edarbyclor)	40/12.5 mg once daily	40/12.5 mg to 40/25 mg once daily	--	--	--	--	--	40/12.5 mg, 40/25 mg tablets
candesartan/ HCTZ (Atacand HCT)	16/12.5 mg once daily	16/12.5 mg to 32/25 mg per day	--	--	--	--	--	16/12.5 mg, 32/12.5 mg, 32/25 mg tablets
irbesartan/ HCTZ (Avalide)	150/12.5 mg once daily	150/12.5 mg to 300/25 mg once daily	--	--	--	--	--	150/12.5 mg, 300/12.5 mg tablets

Dosages (continued)

Drug	Initial hypertension dosage	Hypertension dosage range	Type 2 diabetic nephropathy dosage range	Risk Reduction	CHF	Post MI	Dose for volume- or salt-depleted patients	Availability
Angiotensin II Receptor Blockers: Combination Products								
losartan/HCTZ (Hyzaar)	50/12.5 mg once daily	50/12.5 mg once or twice daily or 100/25 mg once daily	--	--	--	--	--	50/12.5 mg, 100/12.5 mg, 100/25 mg tablets
olmesartan/ HCTZ (Benicar HCT)	20/12.5 mg once daily	20/12.5 mg to 40/25 mg once daily	--	--	--	--	--	20/12.5 mg, 40/12.5 mg, 40/25 mg tablets
sacubitril/ valsartan (Entresto)	--	--	--	--	Initial: 49/51 mg twice daily; Range: 24/26 mg to 97/103 mg twice daily‡	--	--	24/26 mg, 49/51 mg, 97/103 mg tablets
telmisartan/ HCTZ (Micardis HCT)	40/12.5 mg once daily	40/12.5 mg to 160/25 mg once daily	--	--	--	--	--	40/12.5 mg, 80/12.5 mg, 80/25 mg tablets
valsartan/HCTZ (Diovan HCT)	160/12.5 mg once daily	80/12.5 mg to 320/25 mg once daily	--	--	--	--	--	80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, 320/25 mg tablets

Maximal clinical effects of combination therapy are seen 2 to 4 weeks after a dosage adjustment.

* Pediatric suspension may be compounded for pediatric patients.

† Manufacturer recommends correcting condition prior to initiating treatment, or that therapy is initiated under close medical supervision with consideration given to administration of a lower dose of candesartan.

‡ For sacubitril/valsartan (Entresto), a reduced starting dose of 24/26 mg twice daily is recommended for patients not currently taking an ACE inhibitor or ARB or previously taking a low dose or these agents; patients with severe renal impairment; and patients with moderate hepatic impairment.

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this category. Randomized, controlled trials comparing agents within this class for approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Some antihypertensive comparative trials of short duration have been conducted between the ARBs. Long-term clinical outcomes trials have not directly compared the agents in this class. Cardiovascular outcomes data are available from large clinical trials comparing an ARB to another type of antihypertensive agent.

Hypertension

azilsartan (Edarbi) versus olmesartan (Benicar)

In a randomized, double-blind, placebo controlled trial of 1,275 patients, azilsartan was compared to olmesartan.[174] The primary endpoint was change from baseline in mean 24-hour ambulatory systolic blood pressure (SBP) after 6 weeks of treatment. Patients had an initial SBP of 130 mm Hg to 170 mm Hg. Treatment arms included: placebo, azilsartan 20 mg, 40 mg, and 80 mg, and olmesartan 40 mg. Reduction in 24-hour mean SBP was greater with azilsartan 80 mg than olmesartan 40 mg (-2.1 mm Hg, p=0.038), while azilsartan 40 mg was found to be non-inferior to olmesartan 40 mg.

azilsartan (Edarbi) versus valsartan (Diovan) versus olmesartan (Benicar)

A randomized, double blind study compared 2 doses of azilsartan (40 mg and 80 mg) with valsartan 320 mg, olmesartan 40 mg, and placebo[175]. The primary endpoint was change from baseline in 24 hours mean SBP. This study included 1,291 patients with baseline 24 hour mean SBP of 145 mm Hg. Azilsartan 80 mg demonstrated superior efficacy to both valsartan at 320 mg (-10 mm Hg, p<0.001) and olmesartan at 40 mg (-11.7 mm Hg; p=0.009). Safety and tolerability among placebo and the 4 active treatment groups were similar.

azilsartan/chlorthalidone (Edarbyclor) versus olmesartan (Benicar) and hydrochlorothiazide

A randomized, double-blind, 12-week, forced-titration trial of 1,071 patients compared the effect of azilsartan/chlorthalidone (40/12.5 mg or 40/25 mg) to olmesartan medoxomil/HCTZ (40/25 mg) in reducing SBP in patients with moderate to severe hypertension.[176] Both doses of azilsartan/chlorthalidone lowered blood pressure more effectively (p<0.001) versus olmesartan medoxomil/HCTZ at each hour of the 24-hour interdosing period as measured by ambulatory blood pressure monitoring (ABPM). Similar results were observed in all subgroups, including age, gender, or race.

candesartan (Atacand) versus losartan (Cozaar)

Candesartan was compared to losartan in the treatment of essential hypertension in 334 patients using a multicenter, double-blind, placebo-controlled study design.[177] A placebo run-in period was completed for the first 4 weeks of the study. If the patients' sitting diastolic blood pressure (DBP) was between 95 to 114 mm Hg at the end of the placebo run-in, the patient was randomized to candesartan 8 mg (n=82), candesartan 16 mg (n=84), losartan 50 mg (n=83), or placebo (n=85) given once daily for 8 weeks. Blood pressure and heart rate measurements were completed with a fully automatic device during the morning clinic visit and approximately 24 hours after intake of the study drug. The DBP decreased by -8.9 mm Hg with candesartan 8 mg, -10.3 mm Hg with candesartan 16 mg, -6.6 mm Hg with losartan 50 mg, and increased slightly with placebo. The active medications reduced sitting DBP to a greater extent compared to placebo. There was no difference between candesartan 8 mg and losartan 50 mg in reduction in blood pressure. The mean difference between the sitting DBP with candesartan 16 mg and losartan 50 mg was -3.7 mm Hg ($p=0.013$).

Candesartan (16 mg to 32 mg daily) and losartan (50 to 100 mg daily) were compared in 332 patients.[178] In an 8-week, randomized, double-blind, parallel group study, patients had a mean trough DBP of 90 mm Hg or greater following at least 4 weeks of treatment with candesartan 16 mg or losartan 50 mg daily. Doses were then doubled in both groups. Candesartan (-11 mm Hg) provided significantly greater reduction in trough sitting DBP than the losartan regimen (-8.9 mm Hg). Achievement of sitting DBP of less than 90 mm Hg or reduction in BP of greater than 10 mm Hg, defined as a responder, was reported in 64% and 54% of the candesartan and losartan groups, respectively. Discontinuation rate due to adverse effects or lack of efficacy was higher in the losartan group (1.9% for candesartan versus 6.5% for losartan).

Another double-blind, randomized, forced-titration study compared candesartan and losartan in 611 patients with essential hypertension.[179] Patients had DBP of 95 to 114 mm Hg prior to enrollment. Patients were randomized to candesartan 16 mg once daily or losartan 50 mg once daily. After 2 weeks, doses were doubled. Candesartan reduced blood pressure (BP) at trough (24 hours post-dosing), 6 hours (peak effect), and 48 hours after a dose to a significantly greater degree than losartan ($p<0.05$). The 24-hour trough BP values were reduced by -13.4/-10.5 mm Hg with candesartan and -10.1/-9.1 mm Hg with losartan. Response rates did not differ between the 2 treatments (58.8% for candesartan and 52.1% for losartan). Adverse events were similar between the groups.

A similarly designed study also evaluated candesartan and losartan in 654 hypertensive patients.[180] Trough BP reductions were significantly greater in the candesartan group (-13.3/-10.9 mm Hg) than in the losartan group (-9.8/-8.7 mm Hg, $p<0.001$). Significantly more patients were responders in the candesartan group (62.4 and 54% for candesartan and losartan, respectively; $p<0.05$). Both treatments were well tolerated.

A double-blind, randomized, placebo-controlled study compared candesartan 8 mg to losartan 50 mg once daily for 6 weeks in 256 patients with mild to moderate hypertension.[181] Ambulatory BP measurements were completed every 15 minutes for 36 hours. The mean change in DBP over hours zero to 24 hours after the dose were significantly greater with candesartan (-7.3 mm Hg) compared to losartan (-5.1 mm Hg; p<0.05) and placebo (0.3 mm Hg, p<0.001). The mean change in SBP was also greater with candesartan (-10.8 mm Hg) compared to losartan (-8.8 mm Hg) and placebo (1.2 mm Hg, p<0.001). Candesartan 8 mg was associated with a greater reduction in DBP and SBP, relative to placebo, when compared with losartan 50 mg, during both daytime and night-time, and between 12 and 24 hours after dosing (p<0.001). Candesartan and losartan were well tolerated.

candesartan (Atacand) in pediatrics

Two randomized, double-blind multicenter, 4-week dose ranging studies were conducted to evaluate the effects of candesartan in pediatric patients.[182] In the first study, 193 patients 1 to < 6 years of age, 74% of whom had renal disease, were randomized to receive an oral candesartan 0.05, 0.2, or 0.4 mg/kg once daily. The primary analysis was slope of the change in SBP as a function of dose. Since there was no placebo group, the change from baseline likely overestimates the true magnitude of blood pressure effect. Nevertheless, SBP and DBP decreased 6/5.2 to 12/11.1 mm Hg from baseline across the 3 doses of candesartan.

In the second study, children 6 to < 17 years of age (n=240) were randomized to receive either placebo or low, medium, or high doses of candesartan. For children who weighed < 50 kg the doses of candesartan were 2, 8, or 16 mg once daily. For those > 50 kg, the candesartan doses were 4 mg, 16 mg, or 32 mg once daily. The placebo subtracted effect at trough for sitting SBP/sitting DBP for the different doses were from 4.9/3 to 7.5/7.2 mm Hg. Those enrolled were 47% African American. In children 6 to < 17 years, there was a trend for a lesser blood pressure effect for African Americans compared to other patients. There were too few individuals in the age group of 1 to < 6 years to determine whether African Americans respond differently than other patients to candesartan.

eprosartan versus losartan (Cozaar)

Eprosartan 600 mg once daily and losartan 50 mg once daily were compared in 60 patients with essential hypertension (baseline sitting DBP: 95 to 114 mm Hg) in a double-blind, randomized, 4-week study.[183] Blood pressure was reduced by -12.7/-12.4 mm Hg in the eprosartan group and -10.9/-9.6 mm Hg in the losartan group. A response was reported for 73% of eprosartan-treated patients and 53% of losartan-treated patients.

irbesartan (Avapro) versus losartan (Cozaar)

Following a placebo lead-in phase, a total of 567 patients were randomized in a double-blind manner to 1 of the 4 once-daily dosing treatment arms: placebo, losartan 100 mg, irbesartan 150 mg, or irbesartan 300 mg.[184] The duration of the study was 8 weeks, and baseline characteristics and demographics were comparable for the 4 groups. Results from the study were as follows: irbesartan 300 mg was statistically better than losartan 100 mg in reducing seated DBP (-11.7 and -8.7 mm Hg, respectively; p<0.01), and the antihypertensive effect of irbesartan 150 mg and losartan 100 mg did not differ significantly throughout the study. Conclusions from the study were that the administration of the maximally recommended doses irbesartan and losartan may result in significant differences in blood pressure reductions.

Designed to compare the effectiveness, safety, and tolerability of irbesartan and losartan, the study was a multicenter, randomized, double-masked, elective titration study for patients with mild to moderate hypertension.[185] After a 3-week placebo lead-in phase, 432 patients with a mean DBP of 95 to 115 mm Hg were randomly assigned to receive irbesartan 150 mg once daily or losartan 50 mg once daily. When assessed at week 4, the daily dose of the medications was doubled (to irbesartan 300 mg or losartan 100 mg) if the DBP was greater than 90 mm Hg. At week 8, if the DBP remained greater than 90 mm Hg, HCTZ 12.5 mg once daily was added. In accordance with the prescribing information for losartan, the dose of losartan was decreased to 50 mg once daily when HCTZ was added. A total of 370 patients were evaluable for efficacy. The mean reduction in DBP at week 8 was significantly greater in patients receiving irbesartan monotherapy than in those receiving losartan monotherapy (-10.2 mm Hg versus -7.9 mm Hg, respectively). A greater proportion of irbesartan-treated patients responded to therapy compared to losartan-treated patients (78% versus 64%, respectively). Both regimens were well tolerated.

losartan (Cozaar) in pediatrics

In a double-blind, dose-response study, 175 hypertensive children were stratified by weight and randomized to losartan 2.5 mg to 5 mg (low dose group), 25 mg to 50 mg (middle), or 50 mg to 100 mg (high dose group) for 3 weeks.[186] Children were ages 6 to 16 years. In the first time period during active treatment, sitting trough DBP decreased in a dose-dependent manner (low dose, -6 mm Hg; middle dose, -11.7 mm Hg; high dose, -12.2 mm Hg; p<0.0001). In a second period of the study, patients were randomized to continue on losartan or to undergo a 2-week placebo wash-out period. In the second time period during placebo administration, DBP rose significantly in those patients receiving placebo who previously had been assigned to the middle and high doses of losartan (p=0.003). The manufacturer of losartan sponsored the study.

In 45 hypertensive children with chronic renal parenchymal disorders, the long-term efficacy and safety of losartan in treating hypertension and preserving renal function were evaluated.[187] Nearly all children had hypertension with half having concurrent hypertension and proteinuria. The mean age of the children was 12.85 years, and the mean follow-up was 2.42 years. Compared to baseline, losartan reduced SBP, DBP, and mean arterial blood pressure (MABP) by 9 to 12 mm Hg at the 3-month follow-up visit (all p<0.01). DBP and MABP remained significantly lower at all visits over 1 year (p<0.005 to 0.0014). By the last visit after 1 year of therapy, the percentage of normotensive patients increased significantly compared with baseline (p<0.03 for SBP, p<0.0004 for DBP). For patients with proteinuria, optimal reduction of proteinuria occurred over 3 to 12 months with reductions of 66 to 71% (all p<0.01). The mean glomerular filtration rate (GFR) reduction the year prior to losartan was 9.3 mL/min/1.73 m^2, whereas the mean GFR on losartan saw a reduction of 1.4 mL/min/1.73 m^2 (p=not significant [NS]). No correlation existed between the blood pressure measurements and GFR or magnitude of blood pressure reductions and proteinuria. Eleven percent of patients experienced adverse effects that resulted in discontinuation of therapy.

A 12-week, double-blind, multinational study looked at the effects of losartan 0.7 to 1.4 mg/kg per day compared with placebo (normotensive stratum) or amlodipine 0.1 to 0.2 mg/kg per day up to 5 mg/day (hypertensive stratum) on proteinuria (morning-void urinary protein-creatinine ratio, baseline ≥ 0.3 g/g) in 306 children up to 17 years of age.[188] After 12 weeks of treatment with losartan, proteinuria was significantly reduced compared with amlodipine/placebo (-35.8% [95% CI, -27.6% to -43.1%] versus 1.4% [95% CI, -10.3% to 14.5%], p≤0.001). Significance remained after adjustment for differences across treatment groups in change in BP (losartan produced incremental systolic and diastolic BP reductions versus amlodipine of 5.4 and 4.6 mm Hg, respectively; and versus placebo of 3.8 and 4 mm Hg, respectively). Proteinuria reduction was consistently observed in the normotensive (-34.4% losartan; 2.6% placebo) and hypertensive (-41.5% losartan; 2.4% amlodipine) strata, and in all prespecified subgroups, including age, gender, race, Tanner stage, weight, prior therapy with angiotensin-converting enzyme (ACE) inhibitors or ARBs, as well as among the most common etiologies of proteinuria. Adverse event incidence was low and comparable in all groups.

olmesartan (Benicar) versus losartan (Cozaar) versus valsartan (Diovan) versus irbesartan (Avapro)

Losartan 50 mg, valsartan 80 mg, irbesartan 150 mg, and olmesartan 20 mg given once daily were compared for antihypertensive efficacy in 588 hypertensive patients with DBP of 100 to 115 mm Hg in a randomized, double-blind trial.[189] The majority of patients were male with a mean baseline BP of 157/104 mm Hg. After 8 weeks of therapy following randomization, olmesartan had significantly reduced sitting cuff DBP more than the other agents (olmesartan -11.5 mm Hg, losartan -8.2 mm Hg, valsartan -7.9 mm Hg, and irbesartan -9.9 mm Hg). SBP reductions were similar in all treatment groups. Patients were also evaluated on ambulatory blood pressure monitoring (ABPM).[190] More patients achieved blood pressure less than 140/80 mm Hg by ABPM in the olmesartan group (52.9%) versus losartan (40.3%; p=0.038), valsartan (35.4%; p=0.004), and irbesartan (47%; p=NS).

olmesartan (Benicar) in pediatrics

The efficacy and safety of olmesartan in pediatric patients were evaluated in a randomized, double-blind study involving 302 hypertensive patients aged 6 to 16 years.[191] Hypertension was defined as SBP measured at or above the 95th percentile (90th percentile for patients with diabetes, glomerular kidney disease, or family history of hypertension) for age, gender, and height while off any antihypertensive medication was evaluated. The active treatment phase was conducted in 2 periods, with 2 cohorts in each period (cohort A, 62% Caucasian; cohort B, 100% African American). In period 1, patients were stratified by weight. Patients who weighed 20 to < 35 kg received 2.5 mg (low-dose) or 20 mg (high-dose) once daily and patients who weighed ≥ 35 kg were randomized to 5 mg (low-dose) or 40 mg (high-dose) olmesartan daily for 3 weeks. In period 2, patients maintained their olmesartan dose or were switched to placebo for an additional 2 weeks. Mean changes in seated trough SBP and DBP from the study baseline to the end of period 1 were -7.8/-5.5 mm Hg; -12.6/-9.5 mm Hg for low and high olmesartan doses, respectively, in cohort A, and -4.7/-3.5 mm Hg; -10.7/-7.6 mm Hg for low and high olmesartan doses, respectively, in cohort B. Mean blood pressure reductions were consistently smaller in cohort B than in cohort A. When analyzed by linear regression, a statistically significant olmesartan dose response was observed for seated trough SBP and DBP in cohort A (p=0.0008 and p=0.0026, respectively), cohort B (p=0.0032 and p=0.0125, respectively), and the combined cohorts A+B (p=<0.0001 for SBP and DBP). When adjusted for baseline body weight, a statically significant olmesartan dose response was observed in cohort A (p<0.0001 for SBP and DBP), cohort B (p=0.0265 and p=0.0084 for SBP and DBP, respectively), and cohorts A+B (p<0.0001 for both SBP and DBP). In period 2, blood pressure control decreased in those patients switching to placebo, whereas patients continuing to receive olmesartan therapy maintained consistent blood pressure reduction. The results from the analysis of covariance for the change in seated SBP for cohort A showed a difference between olmesartan and placebo of -3.6 mm Hg (p=0.0093) in favor of olmesartan. This statistically significant effect was also observed for cohorts A+B (-3.16 mm Hg, p=0.0029). Adverse events were generally mild and unrelated to study medication.

telmisartan (Micardis) versus losartan (Cozaar)

In a randomized, double-blind, placebo-controlled, 6-week trial, telmisartan 40 and 80 mg were compared to losartan 50 mg for efficacy and safety.[192] Following a 4-week placebo run-in phase, 223 patients with mild to moderate hypertension were randomized to 1 of the 4 groups. Ambulatory blood pressure monitoring was performed for 24 hours. All groups had significantly lower blood pressure compared to placebo. Telmisartan 40 mg and 80 mg lowered blood pressure significantly more than losartan or placebo at the time period of 18 to 24 hours after dosing ($p<0.05$). All therapies were well tolerated.

telmisartan (Micardis) versus valsartan (Diovan)

In a double-blind, randomized trial, telmisartan and valsartan were compared in 490 patients with hypertension.[193] Following a 2-week washout period, patients were randomized to telmisartan 40 mg to 80 mg daily or valsartan 80 mg to 160 mg daily with forced titration over 8 weeks. Early morning blood pressure was evaluated to determine the blood pressure reduction effects of each product during the last 6 hours of the dosing interval. Ambulatory blood pressure readings for the last 6 hours of the dosing interval were lower with telmisartan than valsartan (SBP: –11 versus –8.7 mm Hg, respectively; p=0.02; DBP: –7.6 versus –5.8 mm Hg, respectively, p=0.01). A second portion of the study included a placebo dose administered to mimic a missed dose. Both products reduced the blood pressure to a similar extent following the "missed dose" or after nearly 48 hours since the previous dose. Adverse events were similar between the 2 groups.

Similar findings were observed in 2 identically-designed randomized, double-blind, forced-titration studies with 887 hypertensive patients.[194] Telmisartan 40 to 80 mg daily and valsartan 80 mg to 160 mg daily were given for a total of 8 weeks. After 4 weeks on the higher dose, a dose of placebo was administered or active therapy. In another 2 weeks, crossover was performed to simulate a missed dose. Following active therapy, DBP was reduced by -7.6 mm Hg and -5.8 mm Hg with telmisartan and valsartan, respectively (p=0.0044). The last 6 hours mean SBP was reduced by -11.1 mm Hg and -9.1 mm Hg with telmisartan and valsartan, respectively (p=0.0066). After the missed dose, the 24-hour mean SBP/DBP was significantly reduced with telmisartan (-10.7/-7.2 mm Hg) compared with valsartan (-8.7/-5.5 mm Hg; for SBP, p=0.0024; for DBP, p=0.0004).

valsartan (Diovan) versus losartan (Cozaar)

Comparison of the antihypertensive efficacy of valsartan and losartan was the primary objective of an international, multicenter, double-blind, randomized, placebo-controlled, forced-titration study involving 1,369 patients with mild to moderate hypertension.[195] A secondary objective of the study was to compare the safety and tolerability of the 2 drugs. Initially, patients were randomized to receive valsartan 80 mg daily (n=551), losartan 50 mg daily (n=545), or placebo (n=273) for 4 weeks. The need for titration to higher doses of the medications was assessed at the end of the 4 weeks. Of the patients receiving valsartan, nearly 96% required an upward dosage titration to 160 mg, and 95.5% of patients receiving losartan required an upward dosage titration to 100 mg daily. A successful response to therapy was defined as a mean DBP of less than 90 mm Hg or a greater than -10 mm Hg decrease in the mean DBP compared to baseline. All dosages of the medications studied were statistically significantly superior to placebo. Valsartan 80 mg and 160 mg daily were as effective as losartan 50 mg and 100 mg in the treatment of mild to moderate hypertension. In addition, the responder rates for patients receiving valsartan 160 mg were statistically superior (p=0.021) to losartan 100 mg daily. Both drugs were safe and well tolerated with an overall incidence of adverse events comparable to placebo.

Losartan and valsartan were compared in a 12-week study involving mild to moderate patients with hypertension.[196] Patients were randomized in a double-blind fashion to losartan 50 mg daily or valsartan 80 mg daily for 6 weeks. After 6 weeks, if the DBP was greater than 90 mm Hg, the dose was doubled for the remainder of the study period. Patients (n=465) were evaluated at week 12 for the mean trough SBP. SBP reduction was similar between losartan (-9.9 mm Hg) and valsartan (-10.1 mm Hg). Patients achieving blood pressure reduction goals were 57% for losartan and 59% for valsartan. Both therapies were well tolerated.

valsartan (Diovan) in pediatrics

A study enrolled 261 hypertensive pediatric patients' ages 6 to 16 years. Patients who weighed < 35 kg received 10 mg, 40 mg, or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥ 35 kg received 20 mg, 80 mg, and 160 mg of valsartan daily (low, medium and high doses).[197] Renal and urinary disorders, and essential hypertension with or without obesity, were the most common underlying causes of hypertension in children enrolled in the study. At the end of 2 weeks, valsartan reduced both SBP and DBP in a dose-dependent manner. Overall, the 3 dose levels of valsartan (low, medium, and high) significantly reduced SBP by -8, -10, -12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, SBP at trough was -4 and -7 mm Hg lower than patients who received placebo treatment. In patients receiving low dose valsartan, SBP at trough was similar to that of patients who received placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

Efficacy and safety of valsartan were studied in 90 pediatric patients' ages 1 to 5 years (mean age of 3.2 years). The study population was 60% male, and 30% were African American.[198] Patients were randomly assigned to low-, medium-, or high-dose valsartan for 2 weeks (phase 1) and then randomly reassigned to placebo or remained on the same valsartan dose for 2 additional weeks (phase 2). Afterward, patients were enrolled into a 52-week, open-label phase where valsartan was dosed to achieve SBP less than 95th percentile. Statistically significant reductions in SBP and DBP of approximately 8.5 mm Hg and 5.7 mm Hg, respectively, were observed at the end of phase 1 in all of the valsartan dose groups. SBP and DBP were also significantly lower during phase 2 in valsartan patients versus placebo. SBP less than 95th percentile was achieved in 77.3% of patients during the open-label phase. Valsartan was well tolerated, and no effects on growth and development were observed. Adverse events occurred at similar frequencies in each of the 3 dose groups in phase 1 and at equal frequencies in the valsartan and placebo arms in phase 2. Serious adverse events and drug-related adverse events occurred infrequently during both the double-blind (2.2% and 5.6%, respectively) and open-label (14.8% and 6.8%, respectively) portions of the study. This was the first trial of an antihypertensive agent conducted in children < 6 years of age.

angiotensin II receptor blockers and the addition of hydrochlorothiazide or chlorthalidone

The addition of hydrochlorothiazide (HCTZ) or chlorthalidone to an ARB has been shown to potentiate its antihypertensive effect as compared to the ARB alone.[199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219]

Diabetic Nephropathy

candesartan (Atacand) versus placebo

Three randomized trials of the DIRECT (Diabetic Retinopathy Candesartan Trials) Program were used to determine whether candesartan affects microalbuminuria incidence or rate of change in albuminuria in patients with type 1 and 2 diabetes.[220] Patients with type 1 (n=3,326) or type 2 (n=1,905) diabetes in 309 secondary care centers were randomized to candesartan 16 mg/day increasing to 32 mg/day versus placebo. Most patients were normotensive, and all had normoalbuminuria (median urinary albumin excretion rate, 5 mcg/min). Patients, caregivers, and researchers were blinded to treatment assignment, and patients were followed for a median duration of 4.7 years. Urinary albumin excretion rate was assessed annually by 2 overnight collections. If urinary albumin excretion rate was 20 mcg/min or greater, then 2 further urine collections were done. The primary endpoint was new microalbuminuria (3 or 4 collections of urinary albumin excretion rate ≥20 mcg/min). The secondary endpoint was rate of change in albuminuria. Individual and pooled results of the 3 trials showed that candesartan had little effect on risk for microalbuminuria (pooled hazard ratio, 0.95; 95% CI, 0.78 to 1.16; p=0.6). Pooled results showed that the annual rate of change in albuminuria was 5.53% lower (95% CI, 0.73% to 10.14%; p=0.024) with candesartan than with placebo.

irbesartan (Avapro) versus placebo

Two large irbesartan trials in diabetic nephropathy are IDNT (versus amlodipine and placebo over 2.6 years) and IRMA-2 (versus placebo over 2 years). The renoprotective effect appears not to be directly related to blood pressure reduction alone.

IDNT: Irbesartan 300 mg daily was compared to amlodipine 10 mg daily and placebo for the effect on progression of diabetic nephropathy in 1,715 type 2 diabetic hypertensive patients.[221] The target blood pressure was 135/85 mm Hg or less in all groups. In the double-blind, randomized trial, the primary endpoints were doubling of baseline serum creatinine concentration, development of ESRD, or death from any cause. The mean duration of follow-up was 2.6 years. Evaluating all the primary outcome measures as a group, irbesartan was associated with a 20% lower risk versus placebo (p=0.02) and 23% lower risk versus amlodipine (p=0.006). Each of the primary endpoints was evaluated separately to show similar findings. A slower increase in serum creatinine concentration in the irbesartan groups over the placebo and amlodipine groups was observed. The progression to ESRD trended lower in the irbesartan groups versus the other 2 groups (both p=0.07). Death was not statistically different among the groups. An evaluation of the CV outcomes was also performed on the study population.[222] Overall, the 3 groups were similar for the composite outcome of CV death, MI, CHF, stroke, and coronary revascularization. A trend in the reduction of the number of strokes was seen with amlodipine (p=0.18). Amlodipine patients had significantly fewer MI events (p=0.02). Irbesartan patients had significantly fewer CHF events compared to amlodipine (p=0.004) and placebo (p=0.048).

IRMA-2: In a randomized, double-blind, placebo-controlled trial, irbesartan 150 and 300 mg were evaluated for efficacy in 590 hypertensive type 2 diabetic patients with microalbuminuria for delaying the progression to diabetic nephropathy.[223] Diabetic nephropathy was defined as the persistence of albuminuria in overnight specimens with a urinary albumin excretion rate (>200 mcg/min) and greater than 30% higher than baseline on 2 consecutive occasions. All 3 groups were comparable at baseline. Over the 2-year period, diabetic nephropathy was identified in 5.2% of the irbesartan 300 mg patients (p<0.001 versus placebo), 9.7% of the irbesartan 150 mg group (p=0.081 versus placebo), and 14.9% of the placebo group. After adjusting for baseline level of microalbuminuria and blood pressure reduction achieved, the hazard ratio for diabetic nephropathy with irbesartan 150 mg was 0.56 (p=0.05) and 0.32 with irbesartan 300 mg (p<0.001). The decline in creatinine clearance did not differ among the groups during the study. Blood pressure, measured at trough, was significantly lower in the irbesartan 150 mg and 300 mg groups compared to placebo (143/83, 141/83, and 144/83 mm Hg, respectively; p=0.004 for SBP for both irbesartan groups versus placebo). Irbesartan was associated with a reduction in the urinary excretion of albumin throughout the study with the greatest reduction seen with the 300 mg dose (38% reduction versus 24% reduction with 150 mg, 2% with placebo). Serious adverse events were reported more frequently with placebo (p=0.02).

A substudy of the 133 patients from the IRMA-2 trial evaluated kidney function following the withdrawal of treatment with irbesartan.[224] At the end of the study, the mean arterial blood pressure (MABP) was similar in all groups – 105, 103, and 102 mm Hg for placebo, irbesartan 150 mg, and irbesartan 300 mg groups. Urinary albumin excretion rate was reduced by 8% (p=NS versus baseline), 34%, and 60%, respectively. One month after the withdrawal of all antihypertensives, MABP was unchanged in the placebo group and was significantly increased in both the irbesartan groups (109 and 108 mm Hg, respectively). Urinary albumin excretion rate was increased by 14% in the placebo group, 11% in the irbesartan 150 mg group, and was persistently reduced in the irbesartan 300 mg group (-47%, p<0.005). Authors concluded that irbesartan 300 mg provides persistent renoprotective effects after discontinuation.

Another substudy (n=43) of the IRMA-2 trial found that the effects of irbesartan on 24-hour ambulatory blood pressure monitoring and trough office blood pressure were similar.[225] The reduction in urinary albumin excretion at the end of the study was 0% (-86 to 42), 38% (-14 to 66), and 73% (59 to 82), respectively (overall, p<0.01). Authors concluded that renoprotective effects of irbesartan are not purely dependent on blood pressure reductions.

A different substudy (n=269) of the IRMA-2 trial analyzed the biomarkers of inflammatory activity at baseline and after 1 and 2 years. Irbesartan significantly decreased high-sensitivity C-reactive protein (hs-CRP) with a 5.4% decrease/year versus 10% increase/year with placebo (p<0.001). Fibrinogen decreased 0.059 g/L/year in the irbesartan group versus 0.059 g/L/year increase for placebo (p=0.027). Interleukin-6 (IL-6) showed a 1.8% increase/year with irbesartan versus 6.5% increase/year for placebo (p=0.005). Changes in IL-6 were associated with changes in albumin excretion (p=0.04). Irbesartan 300 mg once daily reduced low-grade inflammation in this population which could in turn reduce the risk of micro- and macrovascular disease.[226]

Another smaller randomized, double-blind trial with 124 hypertensive type 2 diabetic patients with microalbuminuria demonstrated that irbesartan 300 mg daily reduced urinary excretion of albumin and lowered SBP and DBP.[227] Normotensive patients had reduced urinary excretion of albumin.

losartan (Cozaar) versus placebo

Losartan has been studied in the RENAAL trial for 3.4 years demonstrating renoprotective effects compared to placebo. Numerous small trials have been performed with similar results.

RENAAL: Losartan was evaluated in 1,513 type 2 diabetic patients in addition to other antihypertensive treatment for the progression of doubling of serum creatinine concentration, ESRD, or death.[228] In the randomized, double-blind, placebo-controlled trial, patients were randomized to losartan 50 to 100 mg daily or placebo and followed for a mean of 3.4 years. Proteinuria was found to decline in the losartan group but not in the placebo group (p<0.001). The losartan group had significantly less occurrence of doubling of the baseline serum creatinine concentration (25% risk reduction, p=0.006) and progression to end-stage renal disease (28% risk reduction, p=0.002). The incidence of death was similar in both groups. Losartan provides a 16% reduction in the composite endpoint of doubling of serum creatinine, progression to ESRD, or death compared to placebo (p=0.022). In another analysis of the data from RENAAL trial, higher baseline SBP (140 to 159 mm Hg) increased risk for ESRD or death by 38% (p=0.05) compared with those patients with baseline SBP below 130 mm Hg.[229]

A study with losartan demonstrated a significant reduction of 25% in the albumin excretion rate after 5 weeks of losartan therapy in 147 normotensive type 2 diabetic patients with microalbuminuria.[230] The trial was a multicenter, randomized, double-blind, placebo-controlled trial. Patients were randomized to losartan 50 mg or placebo daily for the first 5 weeks, and then losartan was increased to 100 mg daily. Losartan was associated with a 25% relative reduction in urinary albumin excretion after 5 weeks of 50 mg and 34% after10 weeks. Creatinine clearance did not improve over the study period, and blood pressure was only slightly decreased in the normotensive population. Adverse effects were similar between the groups.

The effects of losartan on endothelial function were measured in 80 type 2 diabetics with microalbuminuria and 68 non-diabetic control patients.[231] Diabetic patients were randomized to losartan 50 mg daily or placebo for 6 months in the double-blind trial. Both endothelial dependent and independent vasodilation (both p<0.001) were significantly impaired in the diabetic patients with or without hypertension compared to the control patients. Blood pressure did not significantly change in either group in the study. Urinary mean albumin excretion rate decreased significantly in the losartan group (p<0.001) and increased significantly in the placebo group (p<0.05).

A multicenter, controlled trial followed 285 normotensive patients with type 1 diabetes and normoalbuminuria for 5 years.[232] Patients were randomly assigned to receive losartan 100 mg per day, enalapril (Vasotec®) 20 mg per day, or placebo. The primary endpoint was a change in the fraction of glomerular volume occupied by mesangium in kidney-biopsy specimens. The retinopathy endpoint was a progression on a retinopathy severity scale of 2 steps or more. A total of 90 and 82% of patients had complete renal-biopsy and retinopathy data, respectively. Change in mesangial fractional volume per glomerulus over the 5-year period did not differ significantly between the placebo group (0.016 units) and the enalapril group (0.005 units, p=0.38) or the losartan group (0.026 units, p=0.26), nor were there significant treatment benefits for other biopsy-assessed renal structural variables. The 5-year cumulative incidence of microalbuminuria was 6% in the placebo group, 17% (p=0.01 by the log-rank test) in the losartan group, and 4% (p=0.96 by the log-rank test) in the enalapril group. The odds of retinopathy progression by 2 steps or more was reduced by 65% in the enalapril group (odds ratio, 0.35; 95% CI, 0.14 to 0.85) and by 70% in the losartan group (odds ratio, 0.3; 95% CI, 0.12 to 0.73) when compared to placebo, independently of changes in blood pressure.

telmisartan (Micardis) versus ramipril (Altace)

A pre-specified analysis of renal outcomes of the ONTARGET study, a 56-month, randomized, double-blind, multicenter study of 25,620 patients with controlled hypertension with vascular disease or high-risk diabetes showed that a composite primary renal end point of dialysis, doubling of serum creatinine, and death was similar for telmisartan 80 mg versus ramipril 10 mg, 13.4% versus 13.5%, respectively (HR, 1; 95% CI, 0.92 to 1.09) but was increased with combination therapy 14.5% (HR, 1.09; 95% CI, 1.01 to 1.18; p=0.037).[233] Secondary outcomes of dialysis and doubling of creatinine had similar results. Estimated glomerular filtration rate (eGFR) declined least with ramipril compared with telmisartan (−2.82 [SD 17.2] mL/min/1.73 m^2 versus −4.12 [SD 17.4], p<0.0001) or combination therapy (−6.11 [SD 17.9], p<0.0001). Compared with ramipril, the increase in urinary albumin excretion was less with telmisartan (p=0.004) or with combination therapy (p=0.001). In the study of patients with high vascular risk, telmisartan was similar to ramipril in reducing renal outcomes. Combination therapy worsened renal outcomes and was associated with increased adverse events.

Congestive Heart Failure

candesartan (Atacand) versus placebo

The CHARM trials evaluated the use of candesartan in patients with chronic heart failure.[234] In the randomized, double-blind, controlled set of clinical trials, candesartan and placebo were compared for effects on CV mortality and morbidity. Overall, nearly 7,600 patients with heart failure were enrolled. Candesartan (titrated to 32 mg daily) or placebo were given to patients with preserved left ventricular function (CHARM-Preserved), those patients with intolerance to angiotensin-converting enzyme (ACE) inhibitors (CHARM-Alternative), and in addition to ACE inhibitors (CHARM-Added). Overall, candesartan had a lower all-cause mortality rate than placebo over an approximate 3-year follow-up period (23 versus 25%, respectively; unadjusted hazard ratio 0.91; 95% CI, 0.83 to 1; p=0.055; covariate adjusted 0.9; 95% CI, 0.82 to 0.99; p=0.032).[235] Cardiovascular death or hospitalization related to CHF was significantly less in the overall candesartan group. In those patients with preserved left ventricular function (ejection fraction greater than 40%), candesartan reduced hospitalizations due to CHF (22 versus 24% over 3 years, respectively; unadjusted hazard ratio 0.89; 95% CI, 0.77 to 1.03; p=0.118; covariate adjusted 0.86; 95% CI, 0.74 to 1; p=0.051).[236] In patients who did not tolerate ACE inhibitors due to cough, renal dysfunction, or hypotension, candesartan or placebo were compared.[237] Lower rate of CV death and hospitalization related to CHF were reported with candesartan (33 versus 40%; unadjusted hazard ratio 0.77; 95% CI, 0.67 to 0.89; p=0.0004; covariate adjusted hazard ratio 0.7; 95% CI, 0.6 to 0.81; p<0.0001). For the ACE-intolerant population, the discontinuation rate was similar between candesartan (30%) and placebo (29%). The CHARM-Added trial evaluated the addition of candesartan to ACE inhibitors, beta-blockers, and other CHF treatments.[238] For those patients on candesartan after a median of 41 months, lower CV death and hospitalization for CHF were reported (38 versus 42%; unadjusted hazard ratio 0.85; 95% CI, 0.75 to 0.96; p=0.011; covariate adjusted, p=0.01). Functional NYHA classifications were improved with the use of candesartan.[239] Overall, discontinuations due to adverse effects were more common in the candesartan group.

valsartan (Diovan) versus placebo

The valsartan heart failure trial (Val-HeFT) was conducted in 5,010 subjects to assess the efficacy of adding valsartan (titrated to 160 mg twice daily) to an existing maximized regimen of diuretics, digoxin, beta-blockers, ACE inhibitors, or combinations of these medications.[240] The trial was a placebo-controlled, double-blind, randomized trial, and the major endpoints were mortality and all-cause morbidity and mortality. Other endpoints included hospitalization, ejection fraction, quality of life, symptoms, and NYHA classification. The valsartan group had a 13.2% lower incidence of all-cause morbidity and mortality (p=0.009) and a 27.5% lower hospitalization rate (p<0.001) as compared to placebo. Ejection fraction, symptoms, and NYHA classification, as well as quality of life, improved significantly in the valsartan group as compared to placebo. The greatest benefit was seen in patients receiving valsartan who were not receiving an ACE inhibitor. Patients receiving an ACE inhibitor, valsartan, and a beta-blocker had a worse outcome for heart failure morbidity.

sacubitril/valsartan (Entresto) versus enalapril

PARADIGM-HF: A randomized, double-blind, multinational, trial was conducted in patients with symptomatic CHF (NYHA class II–IV) and systolic dysfunction (LVEF≤40%) comparing sacubitril/valsartan (n=4,187) and enalapril (n=4,212).[241] Patients had to have been on an ACE inhibitor or ARB for at least 4 weeks and on maximally-tolerated doses of beta-blockers. Patients with a SBP < 100 mmHg at screening were excluded. The primary objective was to determine whether sacubitril/valsartan was superior to enalapril alone in reducing the risk of the combined endpoint of CV death or hospitalization for HF. After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice daily, followed by sacubitril/valsartan 100 mg twice daily, increasing to 200 mg twice daily. Patients who successfully completed the sequential run-in periods were randomized to receive either sacubitril/valsartan 200 mg twice daily or enalapril 10 mg twice daily in addition to recommended therapy. The primary endpoint was the first event in the composite endpoint of CV death or hospitalization for HF. The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with sacubitril/valsartan had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the sacubitril/valsartan group and 1,117 patients (26.5%) in the enalapril group (HR in the sacubitril/valsartan group, 0.8; 95% CI, 0.73 to 0.87; p<0.001). Compared to enalapril, in patients with CHF (NYHA Class II-IV) and reduced ejection fraction, sacubitril/valsartan has been able to reduce CV death and first HF hospitalization by about a 20% relative risk reduction and decrease the relative risk of all cause mortality by 16%. The sacubitril/valsartan group had higher proportions of patients with hypotension and angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

Cardiovascular Morbidity and Mortality Reduction

losartan (Cozaar) versus atenolol (Tenormin®)

A double-masked, randomized study of 9,193 patients (ages 55 to 80 years) with essential hypertension and left ventricular hypertrophy (LVH) was conducted to compare the effects of losartan and atenolol on the incidence of CV events including death, MI, or stroke over at least 4 years in the LIFE study.[242] Patients were included if the initial sitting blood pressure was at least 160 to 200/95 to 115 mm Hg with documented LVH. Both losartan and atenolol significantly reduced blood pressure with a mean reduction of -30/-17 mm Hg and -29/-17 mm Hg, respectively. Losartan reduced the overall risk for CV endpoints by 13% (p=0.021). Cardiovascular deaths did not differ between the groups. Fatal and non-fatal stroke risk reduction was 25% with losartan compared to atenolol (p=0.001), and new onset diabetes occurred less frequently in the losartan group. In a predetermined sub-analysis, diabetic patients (n=1,195) were evaluated separately in the LIFE study.[243] Both drugs significantly reduced blood pressure to a similar degree with 85% of the losartan group and 82% of the atenolol group in the diabetic population achieving a DBP less than 90 mm Hg. Losartan reduced the combined risk of CV death, MI, or stroke by 24% compared to atenolol (p=0.031). Losartan also reduced the risk of death from CV causes by 37% compared to atenolol; however, no significant differences in the risk of MI or stroke were found between the 2 groups. Patients with isolated systolic hypertension (n=1,326) also were observed to have a 25% risk reduction in the composite endpoint of CV death, MI, and stroke with losartan over atenolol despite both drugs reducing blood pressure to a similar degree.[244] Regression of LVH with losartan was greater than that observed with atenolol starting within 6 months after initiation of therapy.[245] New onset atrial fibrillation was lower in the losartan group compared with that of the atenolol group despite similar blood pressure reduction (6.8 versus 10.1 per 1,000 person-years; RR, 0.67; 95% CI, 0.55 to 0.83; p<0.001).[246] A post-hoc analysis of the LIFE study evaluated the effects of losartan in women.[247] Women in the losartan group had significant reductions in the primary composite endpoint (215 versus 261; HR, 0.82; 95% CI, 0.68 to 0.98; p=0.031), stroke (109 versus 154; HR, 0.71; 95% CI, 0.55 to 0.9; p=0.005), total mortality (HR, 0.77; 95% CI, 0.63 to 0.95; p=0.014), and new-onset diabetes (HR, 0.75; 95% CI, 0.59 to 0.94; p=0.015) versus the atenolol group, with no between-treatment difference for MI (HR, 1.02; 95% CI, 0.74 to 1.39; p=0.925), CV mortality (HR, 0.86; 95% CI, 0.64 to 1.14; p=0.282), or hospitalization for HF (HR, 0.94; 95% CI, 0.68 to 1.28; p=0.677). More women in the losartan group required hospitalization for angina (HR, 1.7; 95% CI, 1.16 to 2.51; p=0.007). Risk reductions for the primary composite endpoint, stroke, total mortality, and new-onset diabetes were significantly greater with losartan versus atenolol in women with hypertension and LVH in the LIFE study.

telmisartan (Micardis) versus ramipril (Altace)

ONTARGET was a randomized, double-blind, multicenter study of 25,620 patients with controlled hypertension with vascular disease or high-risk diabetes.[248] After a 3-week single-blind run-in period, patients were randomized to ramipril 10 mg daily, telmisartan 80 mg daily, or a combination of ramipril 10 mg and telmisartan 80 mg daily. The primary composite endpoint of the 56-month study was death from CV causes, MI, stroke, or hospitalization for HF. The primary outcome occurred in 1,412 patients versus 1,423 patients (16.5% versus 16.7%; RR, 1.01; 95% CI, 0.94 to 1.09), in the ramipril versus telmisartan groups, respectively. Telmisartan group had lower rates of cough (1.1% versus 4.2%; p<0.001) and angioedema (0.1% versus 0.3%; p=0.01), and a higher rate of hypotensive symptoms (2.6% versus 1.7%; p<0.001) compared to ramipril. The rate of syncope was the same in both groups (0.2%). In the combination group, the primary outcome occurred in 1,386 patients (16.3%; RR 0.99; 95% CI, 0.92 to 1.07), and there was an increased risk of hypotensive symptoms (4.8% versus 1.7%; p<0.001), syncope (0.3% versus 0.2%; p=0.03), and renal dysfunction (13.5% versus 10.2%; p<0.001) compared to the ramipril group. Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less adverse events. The combination of the 2 drugs was associated with more adverse events without an increase in benefit.

telmisartan (Micardis) versus placebo

A randomized, double-blind, placebo-controlled, multicenter, 2.5-year study of 20,332 patients with a recent ischemic stroke compared telmisartan 80 mg daily initiated soon after an ischemic stroke to placebo to evaluate the primary outcome of recurrent stroke.[249] Secondary outcomes included major CV events (CV death, recurrent stroke, MI, or new or worsening HF) and new-onset diabetes. The primary outcome of first recurrent stroke occurred in 8.7% in the telmisartan group, as compared with 9.2% in the placebo group (HR, 0.95; 95% CI, 0.86 to 1.04; p=0.23). This nonsignificant difference was consistent across various subtypes of stroke. The number of patients with a major CV event was 13.5% in the telmisartan group as compared with 14.4% in the placebo group (HR, 0.94; 95% CI, 0.87 to 1.01). In addition, telmisartan did not significantly reduce the risk of new onset diabetes (1.7% versus 2.1%; HR, 0.82; 95% CI, 0.65 to 1.04; p=0.10, telmisartan versus placebo, respectively).

Post Myocardial Infarction

valsartan (Diovan) versus captopril versus captopril and valsartan

VALIANT: A double-blind, randomized clinical trial compared valsartan, captopril, and the combination in 14,703 patients with recent (0.5 to 10 days) MI complicated by left ventricular systolic dysfunction, heart failure, or both.[250] The primary outcome measure was death from any cause. Patients were randomized to valsartan (n=4,909) 20 mg twice daily titrated up to 160 mg twice daily, captopril (n=4,909) 6.25 mg 3 times daily titrated up to 50 mg 3 times daily, or the combination (n=4,885) of valsartan (20 mg twice daily titrated up to 80 mg twice daily) plus captopril (6.25 mg 3 times daily titrated up to 50 mg 3 times daily). The median follow up was 24.7 months. Death from any cause was similar among the 3 groups. The secondary endpoints of CV death, recurrent MI, or hospitalization for heart failure were also similar among the 3 groups. The combination arm had lower BP measurements and an increase in reported adverse effects and significantly higher discontinuation rate versus captopril ($p<0.05$). Valsartan was shown to be noninferior to captopril in the study.

META-ANALYSES

A meta-analysis of 11 randomized controlled trials compared telmisartan with losartan in 1,832 patients with hypertension. The main efficacy measures were reduction in DBP and SBP, and therapeutic response of DBP and SBP.[251] Ten trials with 1,792 patients reported reduction in clinic BP; 6 trials with 1,163 patients reported ambulatory BP reduction; 7 trials with 1,675 patients reported therapeutic response of BP. Telmisartan resulted in a significant reduction in clinic DBP (weighted mean difference [MD], 1.52 mmHg; 95% CI, 0.85 to 2.19) and SBP (weighted MD, 2.77; 95% CI, 1.9 to 3.63) compared with losartan. There was also a significant reduction in 24-hour mean ambulatory DBP (weighted MD, 2.49; 0.56 to 4.42) and SBP (weighted MD, 2.47; 95% CI, 0.4 to 4.55) with telmisartan compared to losartan. There was also a significant increase in therapeutic response of DBP (relative risk [RR], 1.14; 95% CI, 1.04 to 1.23) and SBP response (RR, 1.1, 95% CI, 1.01 to 1.2) with telmisartan compared to losartan. Both treatments were well tolerated.

A meta-analysis of 9 studies with 11,007 participants compared the CV mortality of ARBs compared to ACE inhibitors.[252] Overall, there was no different between groups in total mortality (risk ratio [RR], 0.98; 95% CI, 0.88 to 1.1), total CV events (RR, 1.07; 95% CI, 0.96 to 1.19), or CV mortality (RR, 0.98; 95% CI, 0.85 to 1.13). However, there was a slight advantage of ARBs compared to ACE inhibitors in withdrawals due to adverse effects (RR, 0.83; 95% CI, 0.74 to 0.93).

A meta-analysis of 9 trials evaluated the safety and tolerability of combination ACE inhibitor and ARB versus ACE inhibitor in patients with HF or left ventricular dysfunction (LVD).[253] A total of 9,199 patients received combination therapy, and 8,961 patients received an ACE inhibitor only. Patients receiving combination therapy had an increased risk of developing any adverse effect by 2.3% (RR, 1.27; 95% CI, 1.15 to 1.4; $p<0.00001$, inter-study heterogeneity [I^2] = 15.9%, number needed to harm [NNH]=42), hypotension by 1.1% (RR, 1.91; 95% CI, 1.37 to 2.66; $p=0.0002$; I^2 = 26.6%; NNH=89), worsening renal function by 1% (RR, 2.12; 95% CI, 1.3 to 3.46; $p=0.003$; I^2 = 67.3%; NNH=100), and hyperkalemia by 0.6% (RR, 4.17; 95% CI, 2.31 to 7.53; $p<0.00001$; I^2 = 0%; NNH=149). There was no difference in angioedema (RR, 0.88; 95% CI, 0.43 to 1.8; $p=0.72$; I^2 = 0%) or cough (RR, 0.84; 95% CI, 0.65 to 1.09; $p=0.19$, I^2 = 0%). This meta-analysis found the combination of ACE inhibitor and ARB combination therapy to be associated with increased adverse events in patients with LVD compared to ACE inhibitor therapy.

A meta-analysis of 6 randomized comparative trials including 49,924 patients showed no significant differences between ARB and ACE inhibitor on the risk of MI (OR, 1.01; 95% CI, 0.95 to 1.07; p=0.75), CV mortality (OR, 1; 95% CI, 0.98 to 1.08; p=0.23), and total mortality (OR, 1.03; 95% CI, 0.97 to 1.1; p=0.2).[254] Overall, the risk of stroke was slightly lower with ARBs than ACE inhibitor (OR, 0.92; 95% CI, 0.85 to 0.99; p=0.037), the direct ACE inhibitors and ARBs comparison showing a non-significant trend in a similar direction. Statistical heterogeneity among trials was not significant, with a low to null inconsistency statistic, for stroke (p=0.67), MI (p=0.86), CV mortality (p=0.14), and total mortality (p=0.12).

A meta-analysis of 4 randomized trials, comprising a total of 8,152 patients, investigated the effects of ACE inhibitors (1 trial), ARB (2 trials), or both treatments (1 trial) in patients with HF and preserved LVEF.[255] Risk ratios (RR) and 95% CI were calculated using a fixed-effect estimate method in the randomized trials. Compared with placebo or no treatment, treatment with ACE inhibition or ARB was associated with lower rates of hospitalization for HF (RR, 0.9; 95% CI, 0.81 to 0.99; p=0.032), though not CV mortality (RR, 1.01; 95% CI, 0.9 to 1.13; p=0.85). In all 3 studies where these endpoints were combined, the one-year incidence of CV death or hospitalization for HF was lowered by ACE inhibition or ARB (RR, 0.74; 95% CI, 0.58-0.94; p=0.014). Compared with placebo, ACE inhibition or ARB significantly lowered risks of hospitalization for HF and the combined endpoint of CV mortality and hospitalization for HF at 1 year, in patients with HF and preserved LVEF. However, there was no significant effect on mortality during more prolonged follow-up; the width of the 95% confidence limits is compatible with a benefit as large as 10% or a hazard as large as 13%.

A meta-analysis of 10 randomized controlled studies evaluated the effects of ARBs and ACE inhibitors on CV risk in hypertensive type 2 diabetes patients (n=21,871).[256] Specifically, the meta-analysis investigated the incidence of MI, stroke, CV events, and all-cause mortality. ARB/ACE inhibitor therapy did not have a significant reduction in all-cause mortality (HR, 0.91; 95% CI, 0.83 to 1; p=0.062; measure of heterogeneity=I^2=21%) but did result in a significant reduction in CV mortality (HR, 0.83; 95% CI, 0.72 to 0.96; p=0.012; I^2=0.9%). Similarly, there was no reduction in MI (HR, 0.85; 95% CI, 0.53 to 1.37; p=0.511; I^2=66.5%) or stroke (HR, 0.99; 95% CI, 0.85 to 1.15; p=0.855; I^2=0%), but there was a reduction in overall CV events (HR, 0.9; 95% CI, 0.82 to 0.98; p=0.019; I^2= 19.5%).A meta-analysis aimed at evaluating the blood pressure lowering effects and incidences of heart attack, stroke, and death in patients taking hydrochlorothiazide (HCTZ) has been published.[257] Based on 14 studies, including 1,234 patients taking HCTZ, blood pressure lowering with HCTZ was inferior to all other classes, such as ACE inhibitors, ARBs, beta-blockers, and calcium antagonists. Additionally, the meta-analysis concluded that there are no studies or evidence that HCTZ reduces myocardial infarction, stroke, or death.

COMPARATIVE EFFICACY[258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273]

Drug	Dose	SBP Reduction (mm Hg)	DBP Reduction (mm Hg)
azilsartan (Edarbi™)	20 – 80 mg daily	12.1 – 15.5	6.2 – 9.4
candesartan (Atacand)	8 – 32 mg daily	8 – 12	4 – 8
candesartan/ HCTZ (Atacand HCT)	16/12.5 – 32/25 mg daily	14 – 19	8 – 11
eprosartan	200 – 400 mg twice daily	7 – 10	4 – 6
irbesartan (Avapro)	150 – 300 mg daily	8 – 12	5 – 8
irbesartan/HCTZ (Avalide)	150/12.5 – 300/25 mg daily	13 – 21	7 – 12
losartan (Cozaar)	50 – 150 mg daily	5.5 – 10.5	3.5 – 7.5
losartan/HCTZ (Hyzaar)	50/12.5 – 100/25 mg daily	9 – 15.5	5.5 – 9
olmesartan (Benicar)	20 – 40 mg daily	12 – 13	5 – 7
azilsartan/chlorthalidone (Edarbyclor)	40/12.5 – 40/25 mg daily	23 – 43	13 – 20
olmesartan/HCTZ (Benicar HCT)	20/12.5 – 40/25 mg daily	17 – 24	8 – 14
telmisartan (Micardis)	40 – 160 mg daily	9 – 13	6 – 8
telmisartan/HCTZ (Micardis HCT)	40/12.5 – 80/12.5 mg daily	16 – 21	9 – 11
valsartan (Diovan)	80 – 320 mg daily	6 – 9	3 – 6
valsartan/HCTZ (Diovan HCT)	80/12.5 – 320/25 mg daily	14 – 21	8 – 11

Note: Blood pressure reduction data are obtained from prescribing information and, therefore, should not be considered comparative or all inclusive.

SUMMARY

Comparative trials have been conducted between angiotensin receptor blockers (ARBs) for the management of hypertension. According to prescribing information, all ARBs lower blood pressure to a similar degree. Limited data suggest that candesartan (Atacand), valsartan (Diovan), and irbesartan (Avapro) at higher dosages offer greater decreases in blood pressure than losartan (Cozaar). Initial trials indicate that azilsartan (Edarbi) may produce a greater systolic blood pressure lowering effect than some other agents; however, there are no long-term outcomes studies for this agent. ARBs are generally well tolerated.

ARBs have extensive data showing renal protective benefits in hypertensive diabetic patients with microalbuminuria. The benefits are over and above that of blood pressure reduction alone and extend to normotensive diabetic patients, as well. Delay in progression of diabetic nephropathy by ARBs is likely a class effect although more data are needed. Losartan (Cozaar) and irbesartan (Avapro) are both FDA-approved for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension.

Valsartan (Diovan) has been approved for use in heart failure (HF) and for use post-myocardial infarction in patients with left ventricular dysfunction, HF, or both. Candesartan (Atacand) is approved for patients with HF to reduce the risk of cardiovascular (CV) death and to reduce hospitalizations related to HF. Current guidelines recommend ACE inhibitors as the treatment of choice for HF. ARBs are recommended in patients unable to tolerate ACE inhibitors. Sacubitril/valsartan (Entresto) is a combination product of a neprilysin inhibitor and an ARB for the use in patients with chronic HF (NYHA Class II-IV) and reduced ejection fraction (HF*r*EF). In the PARADIGM-HF trial, sacubitril/valsartan was more effective in reducing death from CV causes or first-time HF hospitalization in patients with reduced ejection fraction, than the currently recommended standard HF therapy, an ACE inhibitor. Clinical guidelines recommended that patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or an ARB should be switched to an ARNI to further reduce morbidity and mortality. Sacubitril/valsartan is administered in combination with other standard HF therapies, in place of an ACE inhibitor or other an ARB.

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